

## Track 2: Case Study “Nephrotoxicity in the rat”

### Background

PharmX Inc., a pharmaceutical company develops a series of therapeutics for a life threatening disease. Data generated in subchronic toxicity studies in the rat obtained with the lead compound suggest a risk for tubular nephrotoxicity for a series of compounds.

PharmX decided to set up a research project to develop known, valid biomarkers (BM) for tubular nephrotoxicity in the rat based on available, exploratory BMs.

The envisaged deliverable of this project is a process map on how to develop known, valid BMs allowing to

- (i) do an improved ranking of follow-up compounds in the rat (short term),
- (ii) bridge the BMs into clinical application (mid term), and
- (iii) develop drugs with improved safety profile (long term).

### Questions

(1) What is the profile of an ideal BM?

- Early
- Sensitive
- Specific
- Predictive
- Reproducible
- Robust
- Accurate/precise
- Accessible sample
- Inexpensive
- Biologically/ mechanistically relevant
- Superior to existing markers
- Other?

(2) The path from exploratory to known valid BM

(3) What are the elements of BM validation?

- Technical/Assay
  - Intra- and inter-sample
  - Intra-and inter-laboratory
  - Technical validation of assay
  - Statistical validation plan
  - Mapping to gold standard
  - Other?

- Biological model
  - Intra- and inter-species
  - Demonstration of desired profile
  - Biochemical, mechanistic relevance
  - Other?

(4) Who should be involved in the validation and acceptance of BMs?

- Exploratory BMs
- Probable valid BMs
- Known valid BMs

(5) What is needed for regulatory acceptance of a BM?

(6) Can we reach a consensus about the process map for biomarker validation?

(7) What challenges do we face when bridging BMs derived from preclinical experiments are applied in the clinic?

- Animals
  - Healthy animals models
  - Animal disease models
  - Target organs easily accessible
  - Limited predictivity for humans
    - Potentially different mechanisms
    - Difficulty in making quantitative predictions about toxic effects
    - Verbal feedback not possible
    - Other?
- Human
  - Variability in available population of healthy volunteers
    - Lifestyle
    - Co-medication
    - Predisposition for disease
  - Variability in available patient population
    - Lifestyle
    - Co-medication
    - Predisposition for disease
    - State of disease
  - Peripheral tissues accessible
  - Diseases or disease subtypes may be poorly characterized
  - Verbal feedback possible
  - Patient privacy
  - Other?

**Fig. 1. Proposed Baseline Process Map for Validation of Biomarkers of Preclinical Drug Safety Assessment**

